Received: 11 September 2018 | Revised: 22 January 2019 | Accepted: 1 February 2019

DOI: 10.1111/bcp.13894

SHORT REPORT

Five-year trends in acetaminophen use exceeding the recommended daily maximum dose

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Funding information
Johnson & Johnson

Temporal patterns of acetaminophen use exceeding the recommended daily maximum dosage of 4 g over a 5-year period (4/1/2011–3/31/2016) were evaluated in an online 1-week diary study of 14 434 adult acetaminophen users who also reported acetaminophen use in the previous month. Specific medications taken were identified by list-based prompting; respondents were not required to know their medications contained acetaminophen. Details of use were recorded daily; total daily dosage was determined programmatically. Prevalence of >4 g use over time was modelled and tested for linear changes. The overall prevalence of >4 g use (6.3% of users and 3.7% of usage days) did not change over the 5 years: odds ratio (OR) persons, 1.02 (95% CI, 0.98–1.09); OR days, 0.98 (0.92–1.05). Deviations from label directions were largely unchanged, though concomitant use increased slightly. Thus, over a recent 5-year period, there was no evidence of change in how often acetaminophen use exceeded the labelled maximum daily dose.

KEYWORDS

acetaminophen, dosing behaviour, drug safety, epidemiology, time trends

1 | INTRODUCTION

Acetaminophen is one of the most commonly used medications, taken in a given week by approximately 20% of the US adult population.[1,2] It is an active ingredient in hundreds of over-the-counter (OTC) and prescription (Rx) medications indicated for pain, fever, colds, flu, allergies and sleeplessness.[3] Acetaminophen is considered safe when taken as directed, but in overdose, can cause serious liver injury.[3,4] Many reported overdoses are the result of deliberate self-harm, but a substantial proportion are unintentional; for example, 30% of acetaminophen-related ER visits, amounting to over 23 000 visits annually, are attributed to unintentional overdose.[5] The maximum recommended daily adult dose of acetaminophen has been 4 g.[6]

Reports of unintentional overdosing of acetaminophen led the US Food and Drug Administration (FDA) to convene an Advisory Committee on the subject in 2009.[7,8] Since that time, some analyses have reported declines in acetaminophen-related calls to poison centres and hospital visits.[9,10] It is not known how consumers' use of acetaminophen medications may have changed. A number of initiatives to reduce acetaminophen overdose have been undertaken,[11-16] but it is not clear whether impacts could be discerned from population surveys (see Discussion).

To elucidate potential changes in patterns of acetaminophen dosing, we conducted a national behavioural surveillance study with 7-day medication diaries over a 5-year period from April 2011 to March 2016.[17-19] The overall prevalence of use above the 4-g daily dosing limit during the diary week was 6.3% in a sample of individuals who had also taken acetaminophen during the previous 30 days.[19] Here we describe an evaluation of temporal trends in exceeding 4 g in this dataset.

2 | METHODS

The behavioural surveillance data-collection methods have been described in detail previously.[17,18] All participants consented to be in

D.W.K. and S.S. were the Principal Investigators.

the survey, and their identities were not made available to the investigators. The study was ruled exempt by the Boston University Medical Campus Institutional Review Board.

2.1 | Participants

Respondents were US volunteers aged ≥18 sampled from three nationwide online research panels (Lightspeed Research, Global Marketing Insite, Survey Sampling International), who responded to emails inviting them to participate in the study in return for compensation in the form of points that could be redeemed for consumer goods. Nothing in the invitations indicated that the study concerned acetaminophen. The selection of panel members to be invited was adjusted as needed to match the distribution of the US population, based on region, age, income, sex and race/ethnicity.

Over the 5-year study period, a total of 968 034 invitations were sent (it is not known how many were received or viewed); 166 203 persons visited the enrolment website, 48 291 qualified and consented to participate, 18 628 completed 7 days of diaries and an exit survey, and 14 434 reported acetaminophen use during the diary period; these last comprise the analytical population. While data collection was continuous, the enrolment goals varied, and there was an intentional reduction in annual enrolment over time, from 4410 in the first year to 1380 in the fifth.

2.2 | Data collection

After enrolling, respondents were prompted by email daily for 7 consecutive days to complete the online diary of acetaminophen-containing medication use. The diary included what they had taken and when, using a grid of hours that began at the time they completed the previous day's entry. This enabled computation of the daily dose. To reduce the burden of finding their medications for each diary entry, participants first created a list of medications they had on hand, to which they could add at any time. They selected from a comprehensive list of acetaminophen products organized in a hierarchical structure by indication (pain/fever, cold/flu/sinus, allergy), class (OTC or Rx), and brand or product name. Respondents were not told that the list was limited to acetaminophen-containing medications. No information was obtained about the use of non-acetaminophen analgesics.

2.3 | Analysis

Among the analytical population, there were 59 029 total days of acetaminophen use. Exceeding the label-designated daily maximum of 4 g was measured at both the person level (>4 g on at least one diary day, with a denominator of total users) and the day level (denominator of total usage days). At the person level, the prevalence over time was modelled statistically using logistic regression relating >4 g use to the specific date it occurred. At the day level, to account for the nesting of days within persons, the prevalence was modelled using generalized estimating equations (GEE),[20] which accounts for the

What is already known about this subject

- Acetaminophen is an active ingredient in many prescription and over-the-counter (OTC) medications, and one of the most commonly used analgesics and antipyretics. When taken in high doses, it can cause liver injury.
- Recent reports have documented a prevalence of 6.3% of acetaminophen users taking above the maximum recommended daily dose of 4 g at least once in a given week. Secular trends in use over the limit have not been studied.

What this study adds

- The prevalence of acetaminophen usage above the daily maximum did not change over the period from April 2011 to March 2016, although there was a small increase in concomitant use, which has been associated with exceeding the maximum dose.

TABLE 1 Demographics of 14 434 acetaminophen users included in the 5-year trend analysis

	Overall (*n* = 14 434)		4/2011–3/2012 (*n* = 4410)		4/2015–3/2016 (*n* = 1380)	
	No.	%	No.	%	No.	%
Age (median)	44		46		44	
Sex						
Male	5713	40	1800	41	523	38
Female	8721	60	2610	59	857	62
Ethnicity						
White	10 831	75	3408	77	1029	75
Black	1518	11	397	9.0	150	11
Hispanic	1326	9.2	450	10	104	7.5
Other	759	5.3	155	3.5	97	7.0
Region						
Northeast	2573	18	822	19	241	17
North central	3405	24	1056	24	336	24
South central	5449	38	1613	37	523	38
West	3007	21	919	21	280	20
Education[a]						
<12 years	400	2.8	105	2.4	49	3.6
High school graduate	2405	17	732	17	256	19
Some college	5370	37	1621	37	505	37
College graduate	6224	43	1943	44	565	41

[a]Education level was unknown for 35 subjects (0.2%) overall; 9 (0.2%) in the 4/2011–3/2012 period; and 5 (0.4%) in the 4/2015–3/2016 period.

inclusion of multiple and variable observations (days of acetaminophen use) for participants. We used the logit link function and an exchangeable covariance structure.

Three other deviations from label directions, each of which was associated with an increased likelihood of exceeding 4 g,[18] were evaluated at the day level. *Exceeding the one-time dose* is taking more than the label-directed dose for a single OTC medication occasion. Because the prescribed dose of Rx medications was unknown to us, those were never considered to exceed the one-time dose. *Re-dosing too soon* is taking a subsequent dose of a given medication sooner than the minimum recommended interval. For OTC medications, the interval was determined by the label. For Rx medications, a 4-h dosing interval was used. *Concomitant use* is taking a second acetaminophen medication within the dosing interval of the first.

All trend models were adjusted for the influence of cold/flu and allergy seasons, which have been shown to affect use.[19] Odds ratios (ORs) were calculated to estimate the change per year, and the results are shown graphically with statistically-modelled trendlines.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to

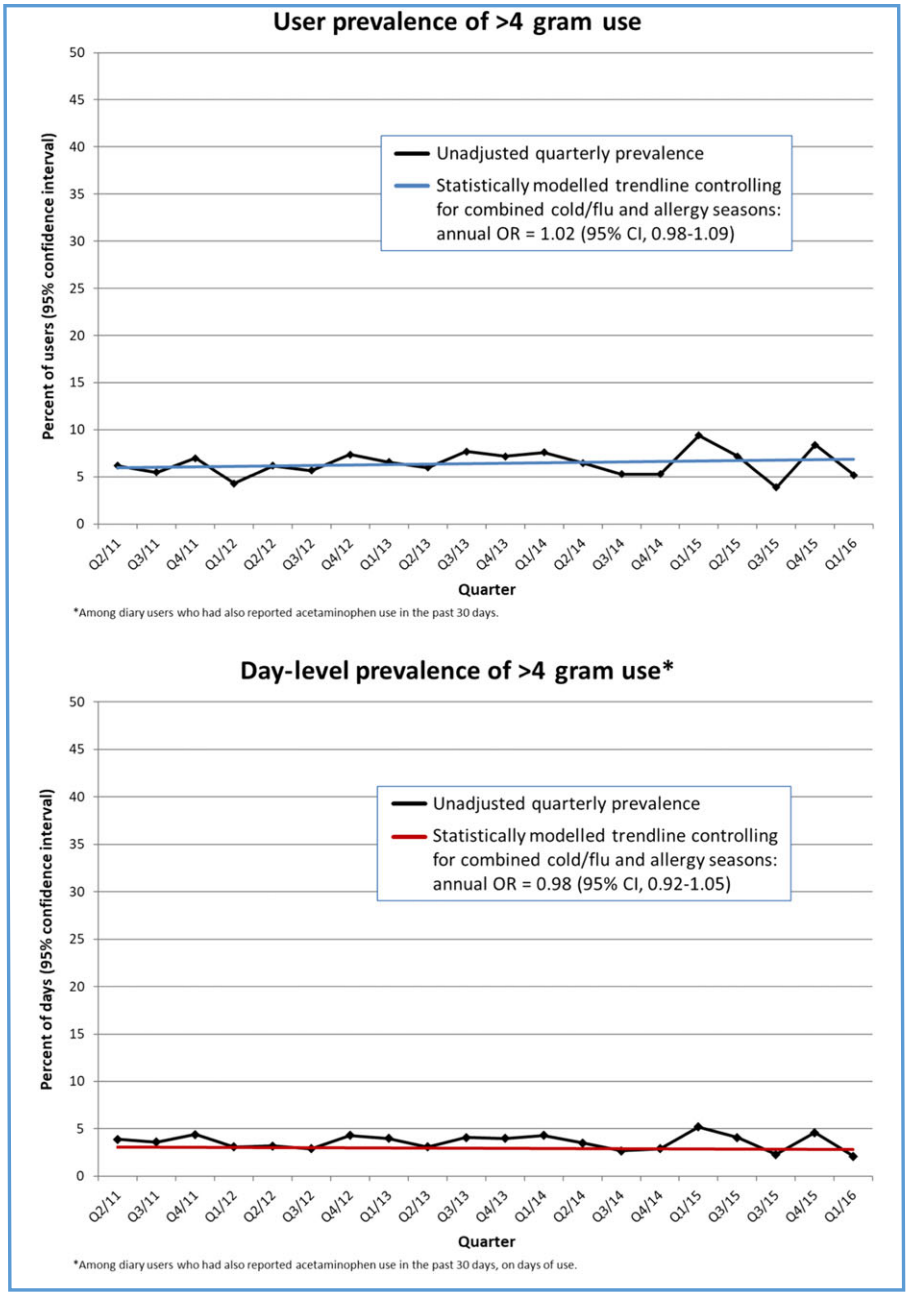

FIGURE 1 Prevalence of exceeding 4 g of acetaminophen in a day, April 2011–March 2016

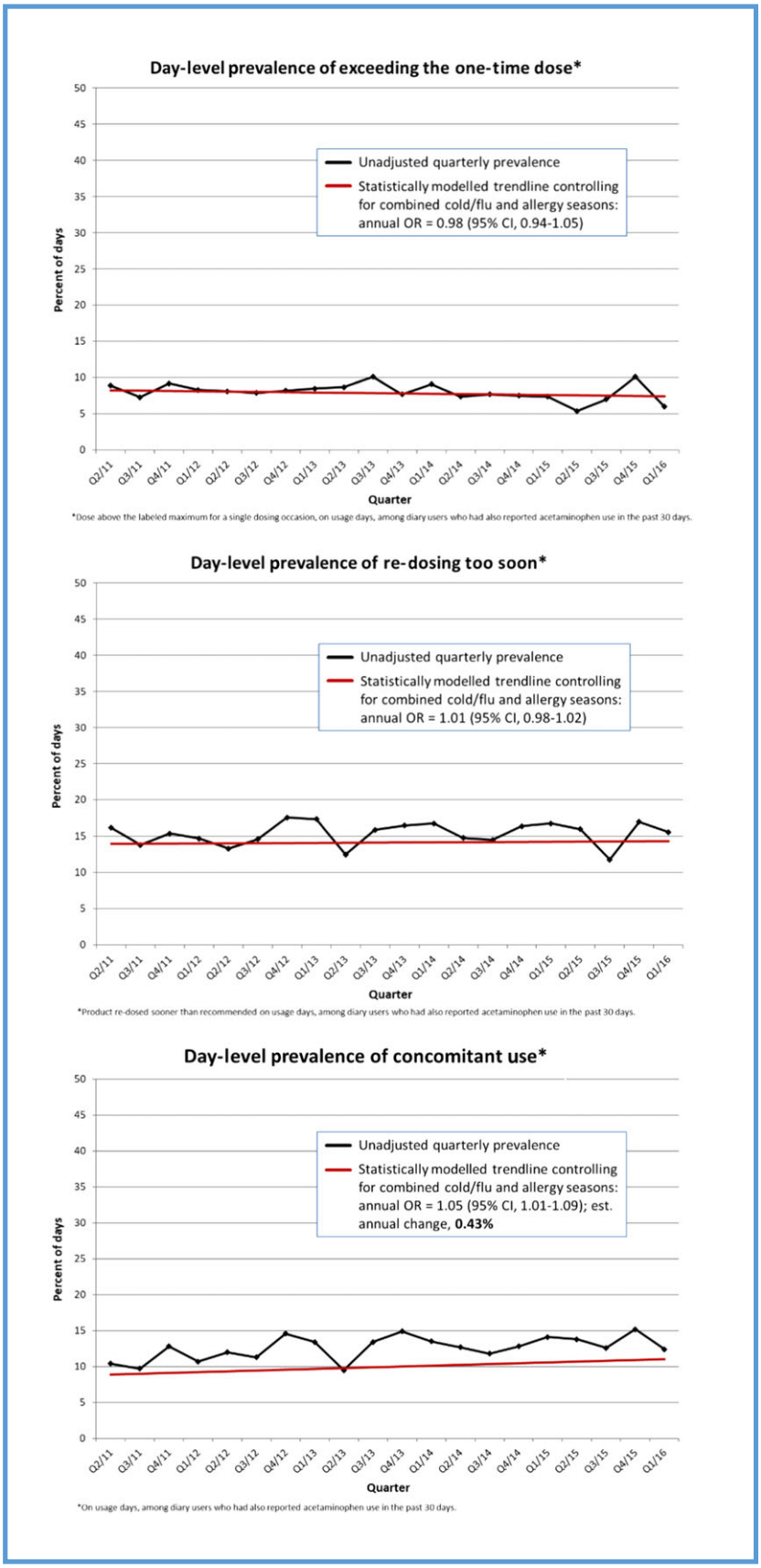

FIGURE 2 Prevalence of dosing deviations associated with exceeding 4 g of acetaminophen in a day, April 2011–March 2016

Pharmacology,[21] and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.[22]

3 | RESULTS

The median age of the subjects was 44 years; 60% were female and 25% non-white; 80% had received education beyond high school (Table 1). This distribution is notable for under-representing those with low educational attainment compared with the US population.[23] There were only minor differences in the composition of the study population between the first and fifth years. The median number of acetaminophen products taken was 1 throughout the study period (data not shown).

The overall prevalence of >4 g use over the 5-year study period was 6.3% among users, and 3.7% among usage days. There were no significant trends in either measure, with annual ORs of 1.02 (95% confidence interval, 0.98–1.09) for users and 0.98 (0.92–1.05) for usage days. The prevalence over time is shown graphically in Figure 1 (scaled to 0–50%). There were also no significant trends in >4 g use on either Rx or OTC usage days, with ORs of 1.00 (0.90–1.11) and 0.98 (0.92–1.04), respectively (results not shown). As shown in Figure 2, there were no significant trends in exceeding the one-time dose or re-dosing too soon; there was a modest increase in the prevalence of concomitant use (OR = 1.05; 95% confidence interval, 1.01–1.09).

4 | DISCUSSION

In this diary-based study of 14 434 acetaminophen users, we found no evidence that the prevalence of exceeding the labelled maximum daily dose of 4 g during a week when acetaminophen was used changed significantly between April 2011 and March 2016. The absence of a trend was apparent both when the unit of analysis was users and when it was days of use. There was a modest increase in concomitant use of two or more acetaminophen products on usage days, which has been associated with exceeding 4 g[18] and therefore might have been expected to lead to an increase in excess use; there were no changes in other intermediate label deviations.

The 5-year surveillance period saw some initiatives undertaken to address the issue of excess acetaminophen dosing, including, but not limited to: launching of industry-sponsored targeted internet campaigns to inform consumers with specific online and purchase behaviours about safe usage[11,12]; reducing the label-recommended maximum daily dose of 500 mg single ingredient OTC products from eight to six pills a day[14,16]; lowering the maximum recommended daily dose of 325 mg single ingredient products and some combination products from 12 to 10 pills[14]; recommending "acetaminophen" to be spelled out on Rx labels[15]; and limiting the acetaminophen strength in Rx products to 325 mg.[13] While we did not observe a corresponding decline in the prevalence of >4 g use, it is important to note that explicit evaluation of the effectiveness of such initiatives was not a goal of the study, and there are various reasons why this would be difficult: potentially limited reach of public education campaigns; a prolonged roll-out of new OTC product labelling; consumers using products that they had on hand with older labels (OTC) or strengths (Rx), or not attending to the changes in instructions. It is also possible that excessive dosing would have increased absent these interventions, and indeed, any impact of the observed small increase in concomitant use may have been partially cancelled out. Survey limitations may also be relevant (see below).

We are not aware of other published reports on secular trends in the prevalence of acetaminophen use over the 4-g limit. Declines in population rates of acetaminophen-related calls to poison centres and hospital visits (up until 2012) have been reported,[9] which have been variously interpreted to reflect increases[9] or decreases[10] in relation to product sales. These findings are not directly comparable with ours, because simply exceeding the 4-g daily limit is not necessarily associated with medical consequences or symptoms—these are usually seen with much higher doses—or with concern sufficient to trigger a call to a poison-control centre.

The overall response rate in the surveillance programme cannot be estimated with precision because it is not known how many of the invited individuals viewed the invitations or were eligible, but it was undoubtedly low, as is common with internet panel surveys. The completion rate (all 7 diary days and the exit survey) of eligible screened subjects was 39%. Low participation could have biased the results if dosing behaviours were related to participation or study completion. However, it has been suggested that internet surveys yield acceptably accurate results, especially as compared with random digit dialing.[24] Furthermore, the privacy of self-completed online surveys has been reported to produce more truthful responses than data collection by interview.[25,26] The study methodology was designed to enhance accuracy, including list-based prompting for medication names, which obviated any need for participants to know that their products contained acetaminophen, and a daily-completed diary that minimized the recall period. While some misclassification in the usage data is certainly possible, there is no reason to believe that it would have varied over time.

A limitation of our results is the relative under-representation of low socioeconomic level individuals. A further limitation is the restriction to those who had taken acetaminophen products in the previous 30 days, which selects more frequent users of the medication; the habits of sporadic users could be different, and may have changed over time, as might the prevalence of 30-day use.

In summary, this large, nationally-based diary study found no evidence of a change in acetaminophen product use exceeding the labelled maximum daily dose of 4 g over a recent 5-year period, despite a small increase in one-dosing behaviour that has been associated with exceeding the limit and some initiatives intended to reduce inadvertent overuse.

ACKNOWLEDGEMENTS

The Behavioral Surveillance Program is conducted with input from a group of external advisors: Neeraj Arora, PhD, MBA, Eric P. Brass, MD, PhD, Heidi M. Jolson, MD, MPH, and Leslie Shifrin.

The authors wish to thank Katherine E. Kelley, MPH, RPh (Slone Epidemiology Center) and Gina Bittner, BS (Pinney Associates) for their assistance with assembling the comprehensive list of acetaminophen products, Steven Pype, BS (Pinney Associates) and Michael Bairos, BS (Slone Epidemiology Center) for computer programming, and the staff at Burke Inc. for their efforts in implementing and managing the data collection.

COMPETING INTERESTS

This work was sponsored by Johnson & Johnson Consumer Inc., which markets TYLENOL®-brand acetaminophen medicines. Decisions about the content and submission were made solely by the authors. D.W.K. received research support from Bayer during the conduct of the study, and has been a consultant to UCB. J.P.K. has no conflicts to report. D.R.B., S.S., and Pinney Associates are consultants to Johnson & Johnson Consumer Inc. and have also consulted to other companies that market competing OTC analgesics. M.K.M. is a consultant to Johnson & Johnson Consumer Inc. R.B.W. is an employee of Janssen Research and Development, LLC. Both Johnson & Johnson Consumer and Janssen Research and Development are part of Johnson & Johnson.

CONTRIBUTORS

S.S. and D.W.K. conceptualized the study. J.P.K. and D.R.B. performed the statistical analyses. All authors oversaw the study and participated in interpretation of the results. D.W.K. drafted the manuscript, and all authors made substantial contributions to its development.

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How to cite this article: Kaufman DW, Kelly JP, Battista DR, Malone MK, Weinstein RB, Shiffman S. Five-year trends in acetaminophen use exceeding the recommended daily maximum dose. *Br J Clin Pharmacol*. 2019;85:1028–1034. https://doi.org/10.1111/bcp.13894